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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/537,088	03/29/00	DWIVEDI	A 82239

HM12/1107

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EXAMINER	
RUSSEL,J	
ART UNIT	PAPER NUMBER
1653	7

DATE MAILED: 11/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/537,088	A. Dwivedi, et al
	Examiner	Group Art Unit
	J. Russel	1653

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 10-4-2001.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-12, 14, and 15 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 1-12, 14, and 15 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

The amino acid sequence at page 3, line 3, of the specification is subject to the sequence disclosure rules, but no sequence listing has been submitted. Further, a SEQ ID NO needs to be inserted after each occurrence of a sequence subject to the sequence disclosure rules. See 37 CFR 1.821(d).

Applicant must provide an original computer readable form (CRF) copy of the Sequence Listing, an original paper copy of the Sequence Listing as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter as required by 37 CFR 1.825(a) and (b).

2. The disclosure is objected to because of the following informalities: Because of insufficient top margins, the first lines of pages 3, 9, 11, and 12 were partially obliterated by hole punching. These lines of the specification will have to be re-submitted by appropriate amendment. Because of poor copy quality, at least portions of page 1, line 21, and page 8, line 1, are illegible. These lines of the specification will have to be re-submitted by appropriate amendment. There is no Brief Description of the Drawings as required by 37 CFR 1.74. At page 1, line 7, there is an incomplete sentence (i.e., "Dimethyl-beta cyclodextrin."). At page 1, line 14, "analgesics" is misspelled. At page 2, lines 12 and 13, there are unmatched beginning brackets. At page 4, line

1, the inverted numeral "4" should be deleted. At page 6, line 4, "hydroxyethyl" should be deleted. At page 13, line 20, commas should be inserted after "brain" and "heart". There is an unmatched end parenthesis at page 13, line 14. At page 13, last line, there is an unmatched beginning parenthesis. At page 14, line 19, it is believed that "peat" should be "peak". The heading "TABLE 4" should be inserted above the table at page 16, lines 3-4. At page 17, line 1, it is believed that "tritan" is a misspelling of "Triton". Also, Applicants are reminded of the necessity of capitalizing all trademarks and including generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. The specification would benefit from further grammatical revision. Appropriate correction is required.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 2, 5-12, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over the Nath et al article in view of Chiesi et al. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. The Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative. Chiesi et al teach forming an inclusion complex of a basic drug and a cyclodextrin such as hydroxypropyl-β-cyclodextrin and dimethyl-β- cyclodextrin. The inclusion complex results in improved storage stability and

enhanced water solubility and bioavailability for the drug. The drug is to be administered orally or parenterally. See, e.g., column 3, lines 15-21; column 8, lines 54-56; and claim 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al in order to form inclusion complexes for pharmaceutical administration because the opioid peptide of the Nath et al article is a basic drug as required by Chiesi et al and because combining the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al would have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and cyclodextrin derivative in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

5. Claims 1-3 and 7-11 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalins, with cyclodextrins, especially β-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. See, e.g., column 1, lines 8-24; column 4, lines 4-11; and column 5, lines 31-36. The European Patent Application '653 does not teach administration of

Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the European Patent Application '653 because the opioid peptide of the Nath et al article is a specific known example of the peptide and enkephalin drugs which are contemplated by the European Patent Application '653 and because administering the opioid peptide of Nath et al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

6. Claims 1, 2, 4, 7-12, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over Hora et al in view of the Nath et al article. Hora et al teach combining polypeptide drugs with cyclodextrins, β-cyclodextrin, including hydroxyethyl-β-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. See, e.g., the Abstract; column 10, lines 31-45, column 11, lines 59-64; column 16, lines 30-32 and 43;

column 18, lines 45-49; and column 26, line 66 - column 27, line 4. Hora et al do not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

7. Claims 1, 7-12, and 15 are rejected under 35 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with β-cyclodextrin. The combination permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid

peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the French Patent '268 because the opioid peptide of the Nath et al article is a specific known example of the analgesic drugs which are contemplated by the French Patent '268, because the French Patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al article because of the French Patent '268's disclosed ability to administer polypeptide hormones, and because administering the opioid peptide of Nath et al transcutaneously in the pharmaceutical formulations of the French Patent '268 would avoid problems of poor absorption after oral administration or of intrusive i.p. administration methods. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

8. Applicant's arguments filed October 4, 2001 have been fully considered but they are not persuasive.

Throughout Applicants' remarks, they have misnamed the opioid peptide recited in their claims. Applicants' remarks name the compound using the word "glycol". However, this is a misspelling, and the word should be "glycyl".

Applicants contend that the compound of the Nath et al article and Applicants' opioid peptide are different compounds. The examiner disagrees. Concerning the "lack of L", "L" is not a chemical substituent but indicates the stereochemistry of the N-terminal amino acid residue. The other possible stereochemistry is "D". The assumption for any amino acid is that it is in the L-configuration unless there is some indication to the contrary. This is because in nature, the L-forms of amino acids are the predominant form. Accordingly, with no "L" or "D" before the "Tyr" in the compound of the Nath et al article, it is presumed to be in the L-configuration and has the same configuration as the tyrosine residue in Applicants' opioid peptide. Concerning the "lack of an additional Ala in the Nath et al compound", the abbreviation "MePhe" in the compound stands for methylphenylalanine. Both the Nath et al article's compound and Applicants' opioid peptide contain a single D-alanine residue and a single N-methylphenylalanine residue. Both compounds are amines (because of the amine groups at their N-termini) and amides (because they have been amidated with isopropylamine). They are the same compounds.

Applicants note that Chiesi et al, the European Patent Application '653, Hora et al, and the French Patent '268 do not disclose Applicants' opioid peptide. The examiner agrees. However, this does not affect the rejections, which are based upon combinations of prior art references applied under 35 U.S.C. 103.

The combination of the Nath et al article and Chiesi et al under 35 U.S.C. 103 is deemed to be proper. The compound of the Nath et al article, which is the same as Applicants' opioid peptide, is a basic drug because it has an amine group at its N-terminus and because it comprises

no charged sidechains. Accordingly, the compound of the Nath et al article is a species of the basic drugs contemplated by Chiesi et al. Chiesi et al do not require the basic drug to be an acid (see Applicants' response page 6, line 10); rather, Chiesi et al require that the basic drug be combined with an acid. The examiner agrees that Chiesi et al desire to increase solubility of the complexes in order to increase their bioavailability (see column 8, lines 54-56). It is not relevant that this motivation to combine the prior art references may not be the same as Applicants'. See MPEP 2144 under "Rationale Different From Applicant's Is Permissible". In any event, the motivation to combine the references provided by Chiesi et al, i.e. enhanced solubility and improved bioavailability, is the same motivation disclosed by Applicants (see, e.g., page 5, lines 1-3, of the specification).

The combination of the European Patent Application and the Nath et al article under 35 U.S.C. 103 is deemed to be proper for reasons analogous to those set forth above. The European Patent Application '653 also discloses that inclusion complexes are formed by cyclodextrins (see, e.g., column 3, lines 43-46). Again, it is not relevant that the motivation to combine the references may not be the same as Applicants'. Applicants' argument that there is no motivation to make the claimed combination since Applicants' opioid peptide is already stable and capable of being absorbed is not understood, as the motivation used to combine the two references is the desirability of forming a nasally administrable composition comprising the compound of the Nath et al article.

The combination of Hora et al and the Nath et al article under 35 U.S.C. 103 is deemed to be proper for reasons analogous to those set forth above. Again, it is not relevant that the motivation to combine the references may not be the same as Applicants'. Hora et al's description of the cyclodextrins as stabilizing polypeptides in order to maintain their activity (see, e.g., column 19, lines 38-60) is synonymous with Applicants' desired results of long duration of activity and improved efficacy.

The combination of the French Patent '268 and the Nath et al article under 35 U.S.C. 103 is deemed to be proper for reasons analogous to those set forth above. Again, it is not relevant that the motivation to combine the references may not be the same as Applicants'. Applicants' argument that there is no motivation to make the claimed combination since Applicants' opioid peptide is already stable and capable of being absorbed is not understood, as the motivation used to combine the two references is the desirability of forming a transcutaneously administrable composition comprising the compound of the Nath et al article.

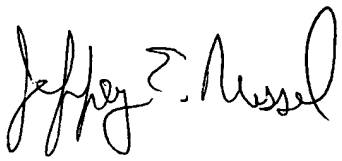
9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Christopher Low can be reached at (703) 308-2923. The fax number for Art Unit 1653 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1653

JRussel

November 6, 2001